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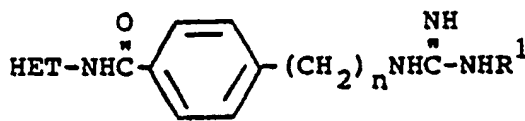
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54 Benzamide protease inhibitors.

57 This application claims a series of compounds of the formula



where HET is a heterocyclic group; n is an integer of 0 to 2 and R¹ is hydrogen or lower alkyl.

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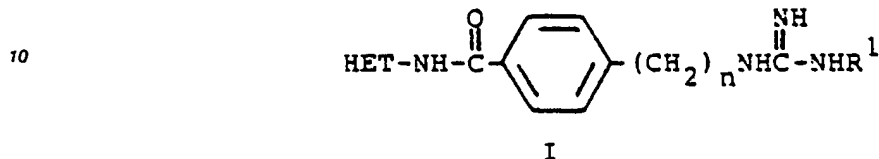
EV 726255925 US

BENZAMIDE PROTEASE INHIBITORS

This invention relates to novel benzamide compounds and, in particular, to a series of N-heterocyclic-4-guanylmethylbenzamide useful as protease inhibitors. These compounds have application as protease inhibitors, in particular as antiplasmin agents.

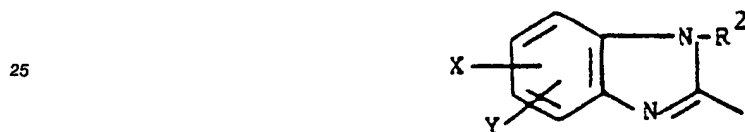
U.S. Patent 4,563,527 claims a series of amidinonaphthyl esters of furoic, benzofuroic and thiophene carboxylic acids as protease inhibitors. U.S. Patent 4,732,916 claims a series of 4-guanylmethylbenzamide derivatives as antiulcer agents.

It has now been discovered that novel compounds of the formula



15 or a pharmaceutically acceptable salt thereof wherein HET is pyrimid-2-yl, dimethylpyrimid-4-yl, thiazol-2-yl, 4-phenylthiazol-2-yl, 4-phenyl-5-carbomethoxythiazol-2-yl, 4-biphenylthiazol-2-yl, pyrazin-2-yl, 6-chloropyrazin-2-yl, quinol-8-yl, 6-methoxyquinol-8-yl, quinol-3-yl, 1,3,4-thiadiazol-2-yl, 3-phenyl-1,2,4-thiadiazol-5-yl, 5-trifluoromethyl-1,3,4-thiadiazol-2-yl, 5-methylisoxazol-3-yl, 5-chloropyrid-2-yl, 4,5-dicyanoimidazol-2-yl, 5-chlorobenzoxazol-2-yl, indazol-5-yl-2-carbomethoxyindol-5-yl or a benzimidazol-2-yl of the formula

20



30 where X is hydrogen or methyl, Y is hydrogen, methyl, benzoyl, nitro, chloro, fluoro, bromo or methoxy and R² is hydrogen, (C₁-C₃)alkyl, phenethyl, phenacyl, N-(C₁-C₃)alkylcarbonylmethyl, N,N-di(C₁-C₃)alkylcarbonylmethyl, N-(C₁-C₃)alkylcarbonyl, (C₁-C₃)alkoxycarbonylmethyl or N-(p-chlorobenzyl)-carbonylmethyl; n is an integer of 0 to 2; and R¹ is hydrogen or (C₁-C₃)alkyl are protease inhibitors, having particular application as inhibitors of serine protease and useful as anti-plasmin and anti-thrombin agents.

35 A preferred group of compounds are those wherein R¹ is hydrogen and n is 0. Especially preferred within this group are the compound where HET is pyrazin-2-yl, pyrimid-2-yl, 1,3,4-thiadiazol-2-yl, quinol-8-yl, thiazol-2-yl or indazol-5-yl.

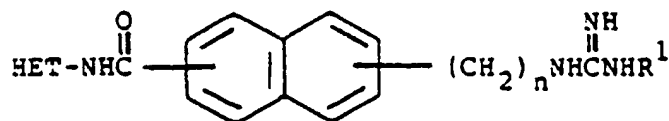
A second group of preferred compounds are those where HET is a benzimidazol-2-yl of the formula



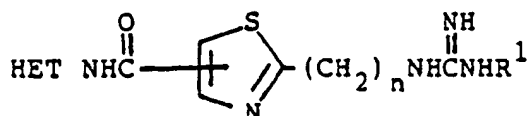
where X is hydrogen. Especially preferred within this group are the compounds where Y and R² are each hydrogen, where Y is 5-nitro and R² is hydrogen, where Y is 5-chloro and R² is hydrogen; or where Y is hydrogen and R² is N,N-diethylcarbonylmethyl.

50 As used herein, the term (C₁-C₃)alkyl defines alkyl having one to three carbon atoms; similar terms can be used to define alkoxy, etc.

Also considered within the scope of the present invention are compounds of the formulae



and



where HET, n and R^1 are as herein defined.

The compounds of the present invention are prepared by the acylation of the appropriate aminoheterocyclic with a carboxy activated benzoic acid derivative.

The activated acid can consist of an acid halide or an activated ester or mixed anhydride. The preferred acylating agent is either the N-hydroxysuccinimide ester or the acid chloride.

The coupling reaction can be achieved by contacting one mole of the appropriate benzoic carboxylic acid N-hydroxysuccinimide ester with from 1 to 2 moles of the requisite aminoheterocyclic and about .01 mole of hydroquinone in a reaction-inert solvent such as dimethylformamide, dimethylsulfoxide, or N-methyl-2-pyrrolidone. The reaction is heated in the dark for about 1 to 36 hours at a reaction temperature of 20-180°C.

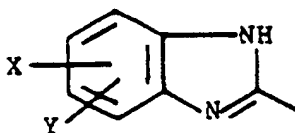
On completion of the reaction, the reaction mixture is diluted with methanol, filtered, if necessary, and the filtrate applied to the protonated form of an ionexchange resin (pH 5-6) such as GC 50 (Aldrich Chemical Co., Inc.). The resin-product complex is then loaded on a column and washed sufficiently with methanol, water, dimethylsulfoxide, dimethylformamide or acetonitrile or mixtures thereof, to remove all the remaining, unreacted aminoheterocyclic.

The product is freed from the resin complex by eluting the column with a 0.1-0.01 molar solution of an acid such as hydrochloric acid, hydrobromic acid, methane sulfonic acid, lactic acid or acetic acid in such solvents as water, methanol or acetonitrile. The wash liquids are combined and concentrated. The product, isolated as the salt of the acid wash, precipitates as the solution is concentrated, and is collected by filtration. Further purification can be carried out by recrystallization from such solvents as dimethylformamide, tetrahydrofuran, ethyl acetate, chloroform, dimethylsulfoxide, N-methyl-2-pyrrolidone, diethyl ether or methanol or mixtures thereof.

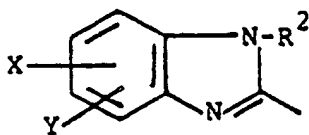
A modification of this procedure comprises contacting one mole of the 4-guanidinobenzoic acid derivative as an acid addition salt with the silylating agent bis-trimethylsilylacetamide, followed by formation of the acid chloride using thionyl chloride. The acid chloride is then treated in tetrahydrofuran with as much as a two-fold excess of the appropriate aminoheterocyclic, or a one fold excess plus an excess of an acid scavenger, such as triethylamine.

After a reaction time of about 30 minutes, at ambient temperatures, the reaction is diluted with sufficient water to precipitate the product, which is recrystallized as previously described.

Compounds of the present invention wherein HET is



are converted to compounds where HET is



where R^2 is as defined, but other than hydrogen.

Acylation of the benzimidazole nitrogen with isocyanates is carried out in a reaction-inert solvent such as dimethylformamide, dimethylsulfoxide, N-methyl-2-pyrrolidone. The reaction can be conducted at from about room temperature to 100°C . Reaction time is about 24 hours and ambient temperatures and 30 minutes to a few hours at elevated temperatures.

When reacting the isocyanate with the compounds identified, it is necessary to use the acid addition salt of the guanidinobenzamide reactant to prevent interaction of the guanyl portion with the isocyanate. Further, it is preferred to use an excess of isocyanate to aid in the completion of the reaction, a ratio of one mole of benzimidazole derivative per five moles of isocyanate provides the desired product.

The reaction mixture, at the end of the reaction period, is diluted with diethyl ether and the precipitated product filtered and purified.

Alkylation of the benzimidazole nitrogen is carried out between one mole of compound containing the benzimidazole moiety and about 5-6 moles of alkylating agent. In addition, the alkylation makes use of from 1 to 4 equivalents of base per mole of starting reagent. Such bases include alkali metal alkoxides and carbonates. The solvent, reaction times and temperature are about the same for the alkylation reaction as for the corresponding acylation reaction.

As previously indicated, the present invention embraces pharmaceutically acceptable salts of the biologically active compounds. Such salts are those which are non-toxic at the dosages administered. Pharmaceutically acceptable acid addition salts include e.g., the hydrochloride, hydrobromide, hydroiodide, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, maleate, mesylate, fumarate, citrate, acid citrate, tartrate, bitartrate, succinate, gluconate and saccharate salts. Conventional methods of forming acid addition salts may be employed.

Plasmin, a serine protease enzyme existing in the blood, is the result of the action of plasminogen activator on the proenzyme plasminogen. Plasmin plays an important role in capillary blood flow and in the dissolution of fibrin. However, when this enzyme is present in abnormal amounts it causes hemorrhagic diseases. In such cases, the use of an anti-plasmin agent is extremely important. The compounds of the present possess this anti-plasmin activity, which can be readily demonstrated by the assay of H. Zimmerman, et al., *Proc. Natl. Acad. Sci.*, 75, 750 (1978).

The compounds of the present invention can be administered as anti-plasmin agents by either the oral or parental routes of administration, with the former being preferred for reasons of patient convenience and comfort. In general, these anti-plasmin compounds are normally administered orally in dosages ranging from about 6 mg to about 400 mg per kg of body weight per day and 1 mg to about 200 mg per kg of body weight per day when given parenterally; variations will necessarily occur depending upon the condition of the subject being treated and the particular compound being administered. It is to be noted that these compounds may be administered in combination with pharmaceutically acceptable carriers by either of the routes previously indicated, and that such administration can be carried out in both single and multiple dosages.

The novel compounds of the invention can be orally administered in a wide variety of different dosage forms, i.e., they may be formulated with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspensions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, such oral pharmaceutical formulations can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for such purposes. In general, the compounds of this invention are present in such oral dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition, in amounts which are sufficient to provide the desired unit dosages.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and calcium phosphate may be employed along with various disintegrants such as starch and preferably potato and tapioca starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often very useful for tableting purposes.

Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection would also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired of oral administration, the essential active ingredient therein may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

The following examples illustrate the invention but are not to be construed as limiting the same.

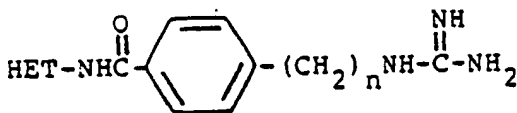
EXAMPLE 1

4-Guanidino-N-(pyrazin-2-yl)benzamide hydrochloride $n = 0$; $R^1 = H$; and HET = 2-pyrazinyl)

A solution of 1.84 g. (19.2 m. mol) of 2-aminopyrazine, 3.0 g. (9.6 m. mol) of 4-guanidinobenzoic acid N-hydroxysuccinimide ester and 300 mg. of hydroquinone in 25 ml. of N-methyl-2-pyrrolidone was heated in the dark under an inert atmosphere at 170 °C for 7 hours. The cooled reaction mixture was diluted with 300 ml. of methanol and 3 ml. of pyridine and treated with 50 g. of CG50 ion exchange resin (H⁺ form). The solution was decanted and treated with an additional 25 g. of resin. The solution was again decanted and treated with 25 g. of resin. The resin fractions were loaded on a column such that the last resin fraction was loaded first, the first, last. The column was eluted with 2 l. of methanol and then with .02 N hydrochloric acid in methanol. The fractions containing the product were combined and concentrated in vacuo to a solid. The residue was dissolved in methanol and precipitated with diethyl ether. The product was filtered, washed with i-propanol and dried, 232 mg., m.p. 278-280 °C.

EXAMPLE 2

Using the procedure of Example 1, except where noted, and starting with the appropriate reagents, the following compounds were prepared as the hydrochloride salt:



HET	n	REACTION TIME	REACTION TEMP. °C	HYDROQUINONE	m.p. °C
benzimidazol-2-yl	0	7 hrs	170	+	265-266
5-NO ₂ -benzimidazol-2-yl	0	7 hrs	170	+	235-237
pyrimidin-2-yl	0	72 hrs	110	-	178-180 ^a
6-Cl-pyrazin-2-yl	0	72 hrs	110	-	273 dec.
2,6-(CH ₃) ₂ -pyrimidin-4-yl	0	120 hrs	110 ^b	-	238 dec. ^a
4-phenyl-thiazol-2-yl	0	5 hrs	110	-	250-252
1,3,4-thiadazol-2-yl	0	5 min	170	-	318-320
3-phenyl-1,2,4-thiadazol-5-yl	0	3 hrs	170	-	308-310 ^a

^a Purified by column chromatography using chloroform-methanol-acetic acid (18:5:1;V:V:V)

^b Solvent dimethylformamide

EXAMPLE 4

4-Guanidino-N-(quinol-8-yl)benzamide (HET = 8-quinolyl; n = 0; and R¹ = H)

A mixture of 200 mg. (.92 m. mol) 4-guanidinobenzoic acid hydrochloride and 190 mg. (.93 m. mol) of bis-trimethylsilylacetamide in 20 ml. of dry tetrahydrofuran was heated at reflux until a solution was achieved, and then cooled to room temperature. Thionyl chloride (380 mg., 1.86 m. mol) was added and the reaction mixture allowed to stir for 5 min. 8-Aminoquinoline (670 mg., 4.64 m. mol) was added in 5 ml. of tetrahydrofuran and the mixture allowed to stir for 30 min. Water (.2 ml) was added to the reaction mixture and the solids filtered and dissolved in 60 ml. of methanol and 120 ml. of chloroform. Addition of diethyl ether precipitated the desired product, 153 mg., m.p. 271-273 ° C.

EXAMPLE 5

Employing the procedure of Example 4, except where noted, and starting with the requisite reagents, the following products were prepared:



HET	EQUIV. AMINE/ACID	REACTION TIME	REACTION TEMP. ° C	m.p., ° C
5-methylisoxazol-3-yl	6:1	30 min	25	242-244
5-chloropyridin-2-yl	6:1	16 hrs	25	255-260
5-trifluoromethyl-1,3,4-thiadiazol-2-yl	7:1	21 hrs	25	326-328
4-phenyl-5-carbethoxythiazol-2-yl	7:1	24 hrs	25	180-185
5-(p-nitrophenylsulfonyl)thiazol-2-yl	5:1	2 hrs	100	285 dec. ^a
thiazol-2-yl	5:1	30 min	25	175 dec.
4,5-dicyanoimidazol-2-yl	5:1	24 hrs ^b	25	211-215
5-chlorobenzoxazol-2-yl	5:1	30 min	25	205-210
4-biphenylthiazol-2-yl	5:1	48 hrs ^c	25	286-288
indazol-5-yl	5:1	48 hrs ^c	25	285 dec.
quinolin-3-yl	6:1	30 min	25	282-285
5-benzoylbenzimidazol-2-yl	5:1	24 hrs ^d	25	235-240
5,6-dimethylbenzimidazol-2-yl	5:1	24 hrs ^d	25	233-237
2-carbethoxyindol-5-yl	6:1	10 min	25	210 dec. ^a

^a Purified by column chromatography using chloroform-methanol-acetic acid (18:5:1;V:V:V).

^b Solvent N-methyl-2-pyrrolidone-tetrahydrofuran (1:5;V:V).

^c Solvent N-methyl-2-pyrrolidone-tetrahydrofuran (1:2;V:V).

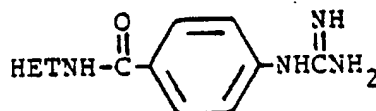
^d Solvent N-methyl-2-pyrrolidone-tetrahydrofuran (1:4;V:V).

EXAMPLE 64-Guanidino-N-(5-chloroimidazol-2-yl)benzamide (HET = 5-chloroimidazol-2-yl; n = 0; and R¹ = H)

A mixture of 970 mg. (4.48 m. mol) of 4-guanidinobenzoic acid and 910 mg. (4.48 m. mol) of bis-trimethylsilylacetamide in dry tetrahydrofuran was heated to reflux for five minutes. After cooling the resulting solution of thionylchloride, 1.07 g. (8.95 m. mol) was added, followed after 20 minutes by the addition of 1.5 g. (8.95 m. mol) of 2-amino-5-chlorimidazole and 1.81 g. (17.9 m. mol) of triethyl amine in 10 ml. of tetrahydrofuran. After 16 hours at room temperature .40 ml. of water was added and the solids filtered, washed with chloroform and recrystallized from methanol-chloroform-diethyl ether, 435 mg., m.p. 263-265 °C.

EXAMPLE 7

Employing the procedure of Example 6, and starting with the appropriate reagents, the following compounds were prepared:



HET	EQUIV AMINE/ACID	EQUIV TEA ^a /ACID	REACTION TIME	REACTION TEMP. °C	m.p., °C
5-bromobenzimidazol-2-yl	2	4	3 hrs	25	265-268
1-methylbenzimidazol-2-yl	2	4	48 hrs	25	265-270
6-methoxyquinolin-8-yl	2	4	30 min	25	280 dec. ^b

^a TEA = triethyl amine.

^b Purified by column chromatography using chloroform-methanol-acetic acid (18:5:1;V:V:V).

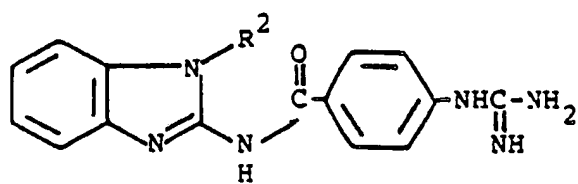
EXAMPLE 8

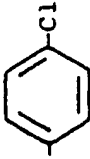
4-Guanidino-N-(1-N-methylcarbamylbenzimidazol-2-yl)benzamide (n = 0; R¹ = H; and HET = 1-(N-methylcarbamyl)benzimidazol-2-yl)

The product of Example 1 (600 mg., 1.81 m. mol) of 520 mg. (9.07 m. mol) of methylisocyanate were added to 10 ml. of dry N-methyl-2-pyrrolidone and allowed to stir at room temperature for 24 hours. The mixture was poured into 200 ml. of diethyl ether and the resulting precipitate filtered and chromatographed on silica gel using chloroform-methanol-acetic acid (18:5:1;V:V:V) as the eluent. The fractions containing the product were combined, concentrated in vacuo to dryness and the residue triturated with methanol, 76 mg., m.p. 188-190 °C.

EXAMPLE 9

Using the procedure of Example 8 and starting with the product of Example 1 and the requisite alkylating agent and base, the following compounds were synthesized:



R ²	BASE	ALKYLATING AGENT	REACTION TIME	REACTION TEMP. °C	m.p., °C
					
CH ₂ CONHCH-	KOC(CH ₃) ₃	ClCH ₂ CONH 4-ClC ₆ H ₄ CH ₂	12 hrs	100	197-200
CH ₂ CON(C ₂ H ₅) ₂	KOC(CH ₃) ₃	ClCH ₂ CON(C ₂ H ₅) ₂	2 hrs	100	220-222
CH ₂ CO ₂ C ₂ H ₅	KOC(CH ₃) ₃	ClCH ₂ CO ₂ C ₂ H ₅	16 hrs	100	210-212 ^c
CH ₂ COC ₆ H ₅	K ₂ CO ₃	ClCH ₂ COC ₆ H ₅	12 hrs	100	241-242 ^c
(CH ₂) ₂ C ₆ H ₅	K ₂ CO ₃	Br(CH ₂) ₂ C ₆ H ₅	16 hrs	100	285-290 ^c
CH ₂ CONHC ₂ H ₅	KOC(CH ₃) ₃	ClCH ₂ CONHC ₂ H ₅	16 hrs	100	240-244 ^c

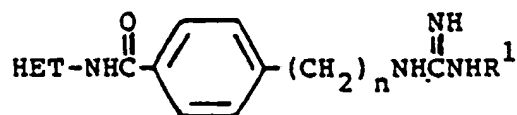
^a Equivalent of base to starting material.

^b Equivalent of alkylating agent to starting material.

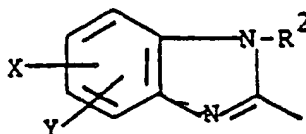
^c Purified by chromatographing using chloroform-methanol-acetic acid (18:5:1;V:V:V).

Claims

1. A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein HET is pyrimid-2-yl, dimethylpyrimid-4-yl, thiazol-2-yl, 4-phenylthiazol-2-yl, 4-phenyl-5-carbethoxythiazol-2-yl, 4-biphenylthiazol-2-yl, pyrazin-2-yl, 6-chloropyrazin-2-yl, quinol-8-yl, 6-methoxyquinol-8-yl, quinol-3-yl, 1,3,4-thiadiazol-2-yl, 3-phenyl-1,2,4-thiadiazol-5-yl, 5-trifluoromethyl-1,3,4-thiadiazol-2-yl, 5-methylisoxazol-3-yl, 5-chloropyrid-2-yl, 4,5-dicyanoimidazol-2-yl, 5-chlorobenzoxazol-2-yl, indazol-5-yl-2-carbethoxyindol-5-yl or a benzimidazol-2-yl of the formula

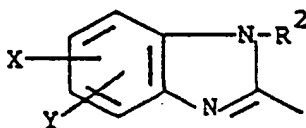


where X is hydrogen or methyl, Y is hydrogen, methyl, benzoyl, nitro, chloro, fluoro, bromo or methoxy and R² is hydrogen, (C₁-C₃)alkyl, phenethyl, phenacyl, N-(C₁-C₃)alkylcarbonylmethyl, N,N-di(C₁-C₃)-alkylcarbonylmethyl, N-(C₁-C₃)alkylcarbonyl, (C₁-C₃)alkoxycarbonylmethyl or N-(p-chlorobenzyl)-carbonylmethyl; n is an integer of 0 to 2; and R¹ is hydrogen or (C₁-C₃)alkyl.

2. A compound of claim 1, wherein R¹ is hydrogen and n is 0.

3. The compound of claim 2, wherein HET is pyrazin-2-yl, pyrimid-2-yl, 1,3,4-thiadiazol-2-yl, quinol-8-yl, thiazol-2-yl or indazol-5-yl.

4. A compound of claim 2, wherein HET is a benzimidazol-2-yl of the formula



wherein, X is hydrogen.

5. A compound of claim 4, wherein Y and R² are each hydrogen.

6. The compound of claim 4, wherein Y is 5-nitro and R² is hydrogen.

7. The compound of claim 4, wherein Y is 5-chloro and R² is hydrogen.

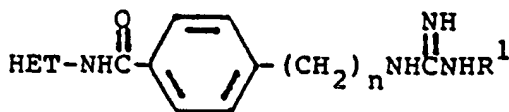
8. The compound of claim 4, wherein Y is hydrogen and R² is N,N-diethylcarbonylmethyl.

9. A compound according to any one of the preceding claims for use in medicine.

10. Use of a compound according to any one of claims 1 to 8 for making a medicament for use as a protease inhibitor.

Claims for the Following States: ES, GR

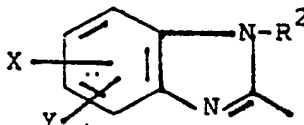
1. A process for preparing a compound of the formula



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wherein HET is pyrimid-2-yl, dimethylpyrimid-4-yl, thiazol-2-yl, 4-phenylthiazol-2-yl, 4-phenyl-5-carbethoxythiazol-2-yl, 4-biphenylthiazol-2-yl, pyrazin-2-yl, 6-chloropyrazin-2-yl, quinol-8-yl, 6-methoxyquinol-8-yl, quinol-3-yl, 1,3,4-thiadiazol-2-yl, 3-phenyl-1,2,4-thiadiazol-5-yl, 5-trifluoromethyl-1,3,4-thiadiazol-2-yl, 5-methylisoxazol-3-yl, 5-chloropyrid-2-yl, 4,5-dicyanomidazol-2-yl, 5-chlorobenzoxazol-2-yl, indazol-5-yl-2-carbethoxyindol-5-yl or a benzimidazol-2-yl of the formula

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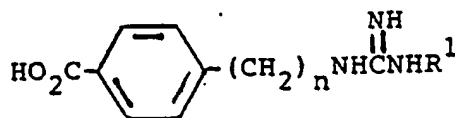
where X is hydrogen or methyl, Y is hydrogen, methyl, benzoyl, nitro, chloro, fluoro, bromo or methoxy and R² is hydrogen, (C₁-C₃)alkyl, phenethyl, phenacyl, N-(C₁-C₃)alkylcarbonylmethyl, N,N-di(C₁-C₃)alkylcarbonylmethyl, N-(C₁-C₃)alkylcarbonyl, (C₁-C₃)alkoxycarbonylmethyl or N-(p-chlorobenzyl)-carbonylmethyl; n is an integer of 0 to 2; and R¹ is hydrogen or (C₁-C₃)alkyl, which comprises acylating a compound of the formula

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HET-NH₂

with a benzoic acid of the formula

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wherein the carboxyl group is activated as an acid chloride, mixed anhydride or active ester, in a reaction-inert solvent in the presence of a catalytic amount of hydroquinone at a reaction temperature of 20-180 °C. and, optionally, preparing a pharmaceutically acceptable salt of the product.

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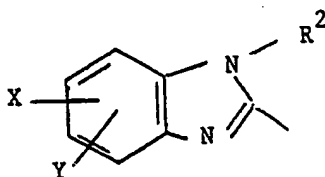
2. A process according to claim 1, wherein R¹ is hydrogen and n is 0.

3. A process according to claim 2, wherein HET is pyrazin-2-yl, pyrimid-2-yl, 1,3,4-thiadiazol-2-yl, quinol-8-yl, thiazol-2-yl or indazol-5-yl.

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4. A process according to claim 2, wherein HET is a benzimidazol-2-yl of the formula

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wherein X is hydrogen.

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5. A process according to claim 4, wherein Y and R² are each hydrogen.

6. A process according to claim 4, wherein Y is 5-nitro and R² is hydrogen.

7. A process according to claim 4, wherein Y is 5-chloro and R² is hydrogen.

8. A process according to claim 4, wherein Y is hydrogen and R² is N, N-diethylcarbonylmethyl.

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	FR-A-2017676 (MERCK & CO, INC.) ---		C07D235/30 A61K31/415
A	GB-A-1122957 (SMITH KLINE & FRENCH LABORATORIES) ---		C07D277/46 C07D277/54
A	US-A-2502528 (RUDOLF MORF (SANDOZ LIMITED)) ---		C07D241/20 C07D215/40
A	US-A-3736330 (PIETER TEN HAKEN (SHELL OIL COMPANY)) ---		C07D285/12 C07D285/08 C07D261/14
A	EP-A-261503 (VALEAS S.P.A. INDUSTRIA CHIMICA E FARMACEUTICA) ---		C07D213/75 C07D233/90 C07D263/58
A	EP-A-1727 (PIERRE FABRE S.A.) ---		C07D209/40 C07D231/56
A	FR-A-1557679 (THE UPJOHN COMPANY) ---		C07D239/42 A61K31/505
A	EP-A-258095 (ROUSSEL-UCLAF) ---		A61K31/425 A61K31/495
A	FR-A-2400516 (ELI LILLY AND COMPANY) ---		A61K31/44 A61K31/47
A	CH-A-570759 (CIBA-GEIGY AG) ---		TECHNICAL FIELDS SEARCHED (Int. Cl.4)
A	GB-A-1551735 (LILLY INDUSTRIES LIMITED) ---		C07D235/00 A61K31/00
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A	PATENT ABSTRACTS OF JAPAN vol. 9, no. 188 (C-295)(1911) 03 August 1985, & JP-A-60 58954 (KUREHA KAGAKU KOGYO K.K.) 05 April 1985, * the whole document *		C07D209/00 C07D231/00 C07D239/00
A	EP-A-196547 (NIHON TOKUSHU NOYAKU SEIZO) ---		
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 28 AUGUST 1989	Examiner DE BUYSER I.A.F.
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A	CHEMICAL ABSTRACTS, vol. 87, no. 23, 05 December 1977 Columbus, Ohio, USA AIDA, KAZUHIKO; SEGAWA, HIROZO (KYOWA GAS CHEMICAL INDUSTRY CO., LTD.): "IMIDAZOLES" page 612; column 1; ref. no. 184,499 V * abstract *		
A	CHEMICAL ABSTRACTS, vol. 85, no. 1, 05 July 1976 Columbus, Ohio, USA SEGAWA, HIROZO; AIDA, KAZUHIKO; TAKAGI, TOSHIAKI (KYOWA GAS CHEMICAL IND.): "2-ACYLAMINO-4,5-DI-CYANOIMIDAZOLES" page 455; column 2; ref. no. 5,638 D * abstract *		TECHNICAL FIELDS SEARCHED (Int. Cl.4)
D,A	US-A-4732916 (TOSHIO SATOH; HITOSHI MATSUMOTO; HISAO KAKEGAWA (KABUSHIKI KAISHA)) -----		
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 28 AUGUST 1989	Examiner DE BUYSER I.A.F.
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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